

consisting of VYAK; VWAK; VEAK; FEAK; VAK; WAK; YAK; FAK; YEK; ELSA; DLYV; and KEASV.

109. A method for ameliorating unwanted immune responses by administering to a subject in
5 need thereof an effective amount of random copolymer wherein said random copolymer
comprises a plurality of amino acid residues selected from:
- (1) hydrophobic, aliphatic residues (leucine, isoleucine, valine, methionine);
 - (2) acidic residues (aspartic acid, glutamic acid);
 - (3) small hydrophilic residues (serine, cysteine, threonine);
 - 10 (4) small aliphatic residues (alanine, glycine); and
 - (5) proline.
110. The method of claim any one of 107-109, wherein the subject is human and the random copolymer is administered at a daily dose of about 22mg per m² of the body surface area of the subject.
- 15 111. The method of claim 107-109, wherein the subject is human and the random copolymer is administered at a weekly dose of about 500mg per m² of the body surface area of the subject.
112. The method of claim 107-109, wherein the subject is human and the random copolymer is administered at a maximum dose of 500mg at time intervals greater than 4 days.
- 20 113. A method of treating a disease that is treatable with a random copolymer comprising administering a composition comprising YEAK (L-tyrosine, L-glutamate, L-alanine and L-lysine), synthesized by solid phase chemistry, in an input molar ratio of about 1.0: 2.0: >6.0>15: 5.0 respectively by administering to a subject a dose effective in ameliorating said diseases.
- 25 114. A kit comprising a premeasured injectable vial containing a composition comprising a random copolymer YFAK and a pharmaceutically acceptable excipient.

115. A kit comprising a premeasured injectable vial containing a composition comprising a random copolymer selected from the group consisting of VYAK; VWAK; VEAK; FEAK; VAK; WAK; YAK; FAK; YEK; ELSA; DLVY; and KEASV and a pharmaceutically acceptable excipient.

5

116. A kit comprising a premeasured injectable vial containing a composition comprising a random copolymer wherein said random copolymer comprises a plurality of amino acid residues selected from:

- (1) hydrophobic, aliphatic residues (leucine, isoleucine, valine, methionine);
- 10 (2) acidic residues (aspartic acid, glutamic acid);
- (3) small hydrophilic residues (serine, cysteine, threonine);
- (4) small aliphatic residues (alanine, glycine); and
- (5) proline;

and a pharmaceutically acceptable excipient.

15

117. The kit of claim 114, wherein the autoimmune disease is selected from the group consisting of multiple sclerosis, type-I diabetes, Hashimoto's thyroiditis, Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus (SLE), gastritis, autoimmune hepatitis, hemolytic anemia, autoimmune hemophilia, autoimmune lymphoproliferative syndrome (ALPS), autoimmune uveoretinitis, glomerulonephritis, Guillain-Barré syndrome, psoriasis, myasthenia gravis, autoimmune encephalomyelitis, Goodpasture's syndrome, Grave's disease, paraneoplastic pemphigus, autoimmune thrombocytopenic purpura, scleroderma with anti-collagen antibodies, mixed connective tissue disease, pernicious anemia, polymyositis, idiopathic Addison's disease, autoimmune-associated infertility, bullous pemphigoid, Sjogren's syndrome, idiopathic myxedema and colitis.

20 118. The kit of claim 114, wherein the disease is an autoimmune disease.

25 119. The kit of claim 114, wherein the disease is multiple sclerosis.

120. The kit of claim 114, wherein the multiple sclerosis is relapsing-remitting multiple sclerosis
121. The kit of claim 114, wherein the disease is mediated by T_H1 cells.
122. A method for conducting a pharmaceutical business, comprising marketing the kit
5 according to any one of claims 106-121 to healthcare providers the benefits of using the kit in the treatment of a disease or disorder.
123. A method for conducting a pharmaceutical business, comprising:
 - (a) manufacturing the kit according to any one of claims 106-121; and
 - (b) marketing to healthcare providers the benefits of using the kit in the treatment
10 of a disease or disorder.
124. A method for treating a disease treatable by administering random copolymer comprising administering to a subject in need thereof a dosing regimen, wherein the random copolymer comprises YEAK (L-tyrosine, L-glutamate, L-alanine and L-lysine) in an output average molar ratio of about 1.0:2.0: 6.0: 5.0 respectively, synthesized by solid phase chemistry, has a length of 52 amino acids, and wherein residues 1-10 of the copolymer sequence has a ratio of about 1.0:2.0: 5.5: 5.0, residues 11-30 have a ratio of about 1.0: 2.0: 6.0: 5.0, and residues 31-52 have a ratio of about 1.0: 2.0: 6.5: 5.0, wherein the dosing regimen inhibits formation of antibodies against the random copolymer.
15
125. A method for treating a disease treatable by administering random copolymer comprising administering to a subject in need thereof a dosing regimen, wherein the random copolymer is selected from the group consisting of VYAK; VWAK; VEAK; FEAK; VAK; WAK; YAK; FAK; YEK; ELSA; DLYV; and KEASV, wherein the dosing regimen inhibits formation of antibodies against the random copolymer.
20
126. A method for treating a disease treatable by administering random copolymer comprising administering to a subject in need thereof a dosing regimen, wherein the random copolymer comprises a plurality of amino acid residues selected from:
25

- (1) hydrophobic, aliphatic residues (leucine, isoleucine, valine, methionine);
- (2) acidic residues (aspartic acid, glutamic acid);
- (3) small hydrophilic residues (serine, cysteine, threonine);
- (4) small aliphatic residues (alanine, glycine); and
- 5 (5) proline. ;

wherein the dosing regimen inhibits formation of antibodies against the random copolymer.

- 127. The method of claim 124, 125, or 126, wherein said method induces peripheral tolerance in the subject to said random copolymer.
- 10 128. The method of claim 124, 125, 126, wherein said method induces central tolerance in the subject to said random copolymers.
- 129. A pharmaceutical composition comprising a random copolymer in a form of microparticles or emulsion.
- 130. The pharmaceutical composition of claim 129, wherein the random copolymer is in an aqueous phase, oil, and emulsifier, wherein the aqueous phase forms an water-in-oil emulsion.
- 15 131. The pharmaceutical composition of claim 129, wherein the random copolymer is suspended in alum.
- 132. The pharmaceutical composition of claim 130, wherein the oil is mineral oil and the emulsifier is sorbitol monolaurate.
- 20 133. The pharmaceutical composition of claim 129, 130, 131, or 132, wherein the random copolymer is YEAK (L-tyrosine, L-glutamate, L-alanine and L-lysine), synthesized by solid phase chemistry, in an input molar ratio of about 1.0: 2.0: 6.0: 5.0 respectively.

134. The pharmaceutical composition of claim 129, 130, 131, or 132, wherein the random copolymer is selected from the group consisting of VYAK; VWAK; VEAK; FEAK; VAK; WAK; YAK; FAK; YEK; ELSA; DLYV; and KEASV.
- 5 135. The pharmaceutical composition of claim 129, 130, 131, or 132, wherein the random copolymer comprises a plurality of amino acid residues selected from:
- (1) hydrophobic, aliphatic residues (leucine, isoleucine, valine, methionine);
 - (2) acidic residues (aspartic acid, glutamic acid);
 - (3) small hydrophilic residues (serine, cysteine, threonine);
 - 10 (4) small aliphatic residues (alanine, glycine); and
 - (5) proline.

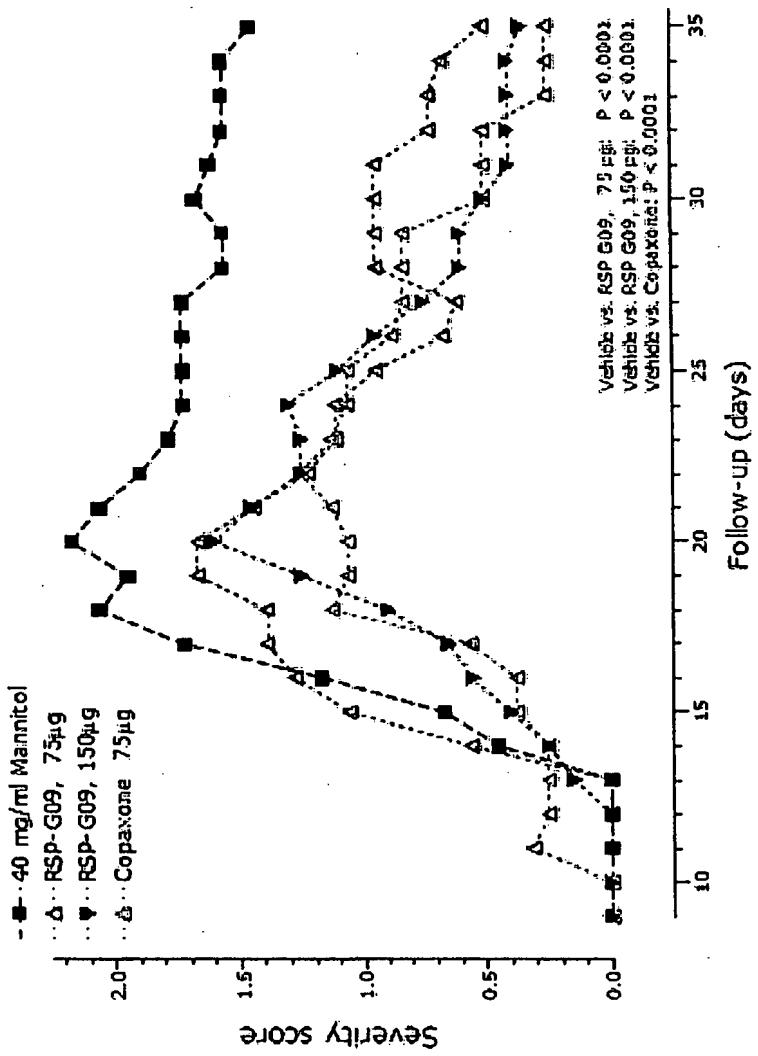
Figure 1**CO-14 efficacy in EAE: disease progression**

Figure 2
Efficacy in EAE: Survival proportions

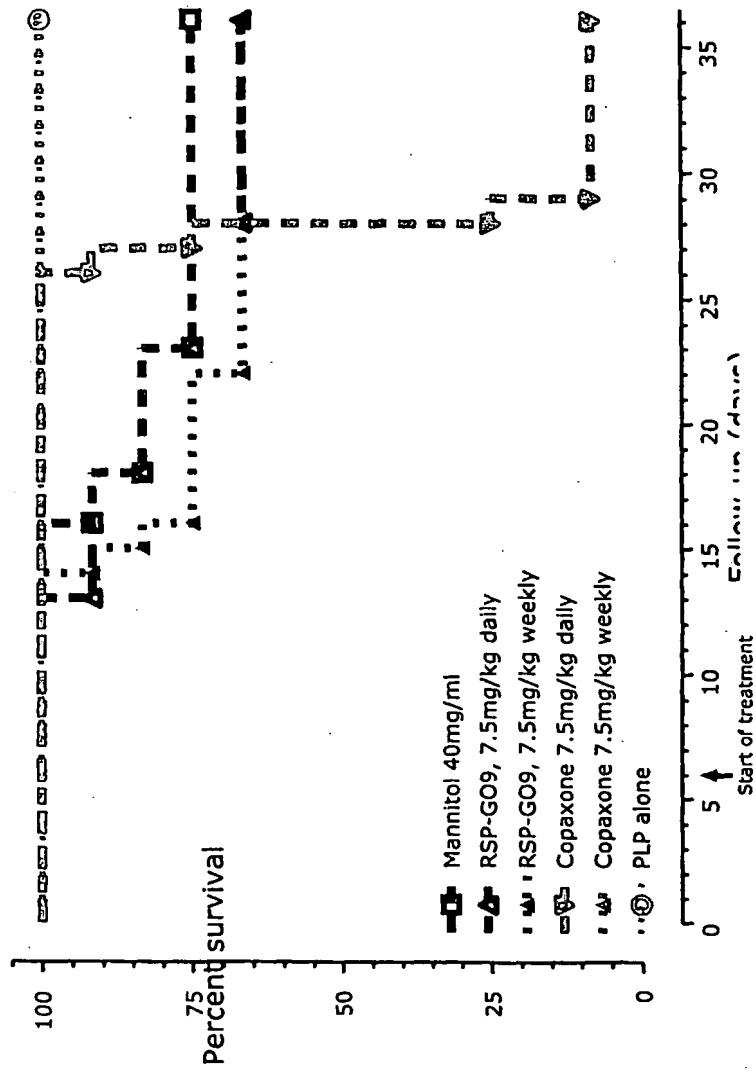


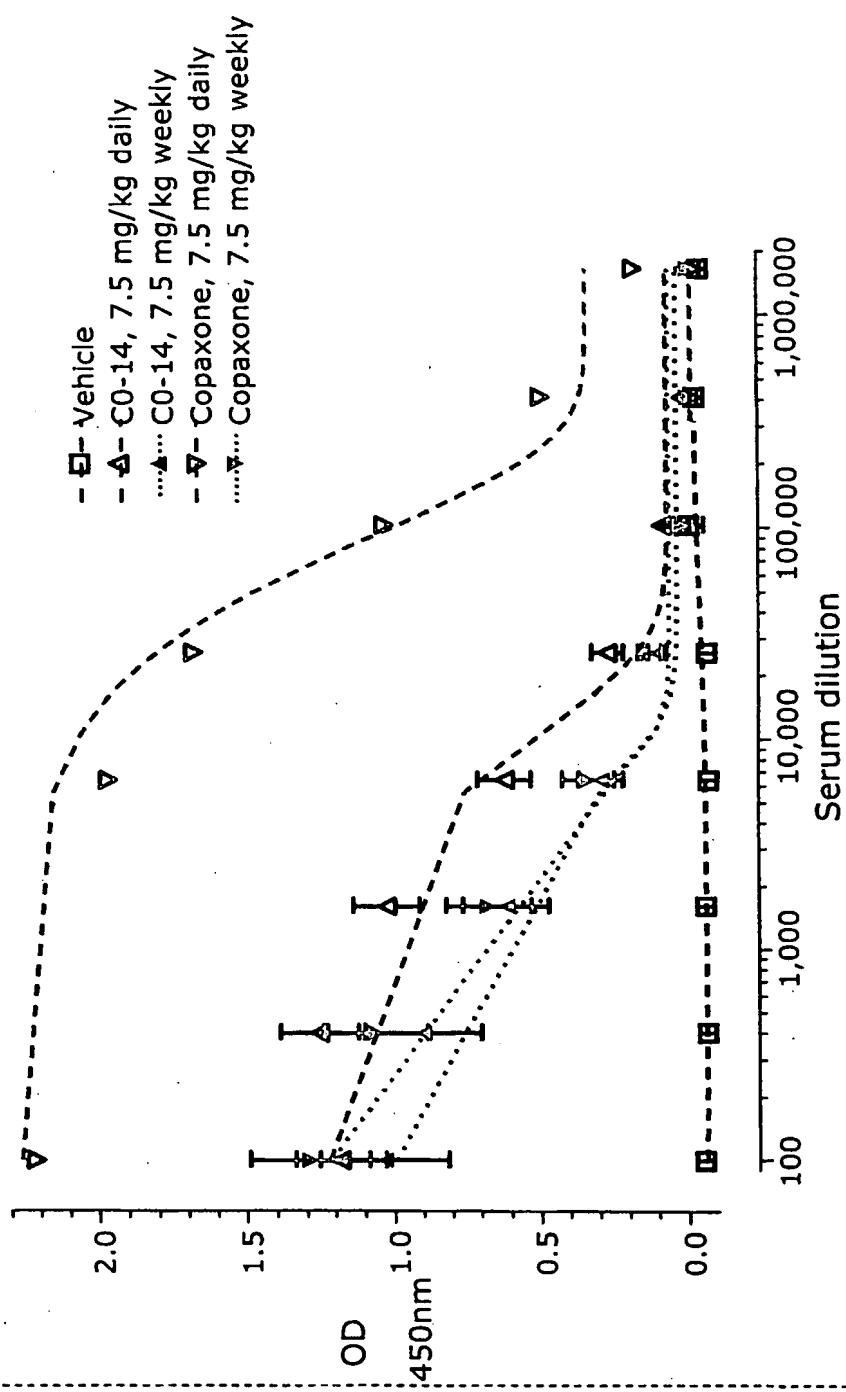
Figure 3**Antibody response against respective Copolymers
- total Ig ELISA, day 37 -**

Figure 4

Antibody response against respective Copolymers
- IgG1 ELISA, day 37 -

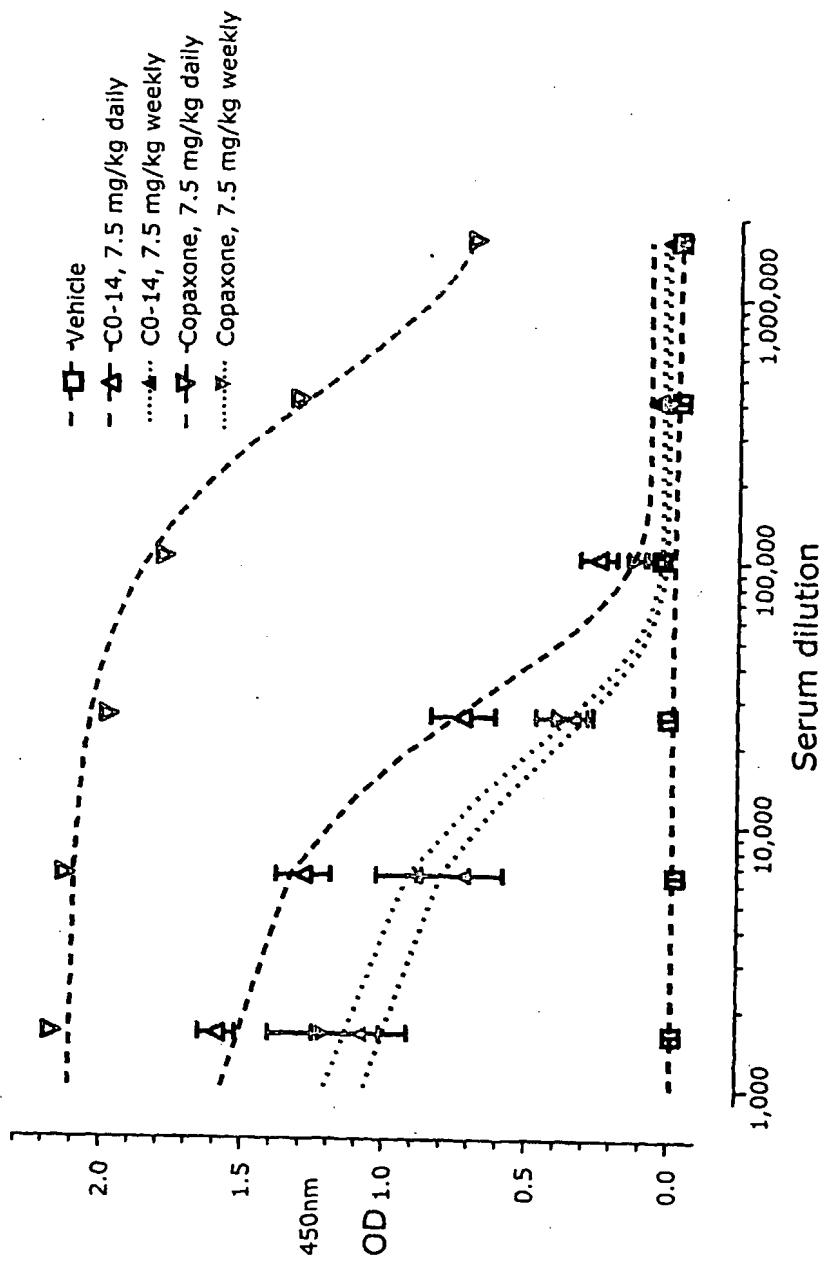


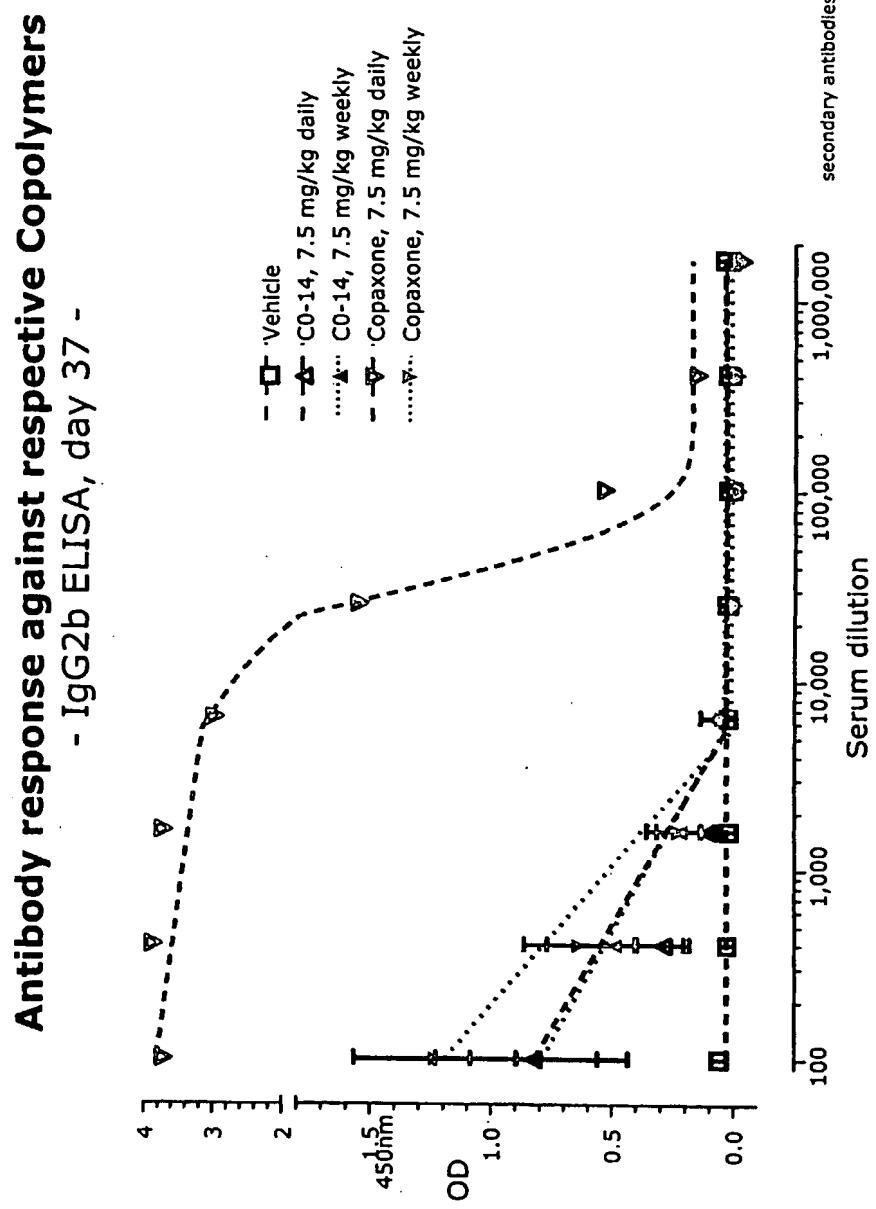
Figure 5

Figure 6

Changes in antibody (IgG) titers against relevant compounds during the course of treatment

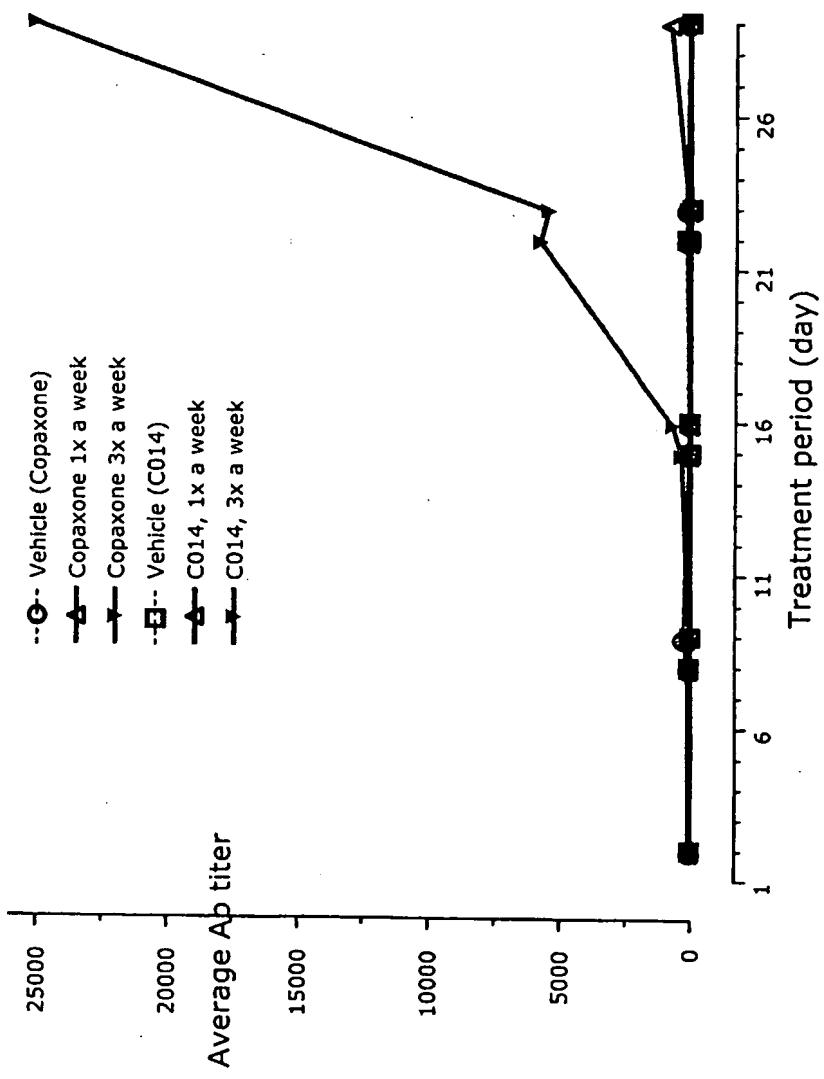


Figure 7

**Antibody response against
autoantigen PLP(139-151)**
- IgG1 ELISA, day 37 -

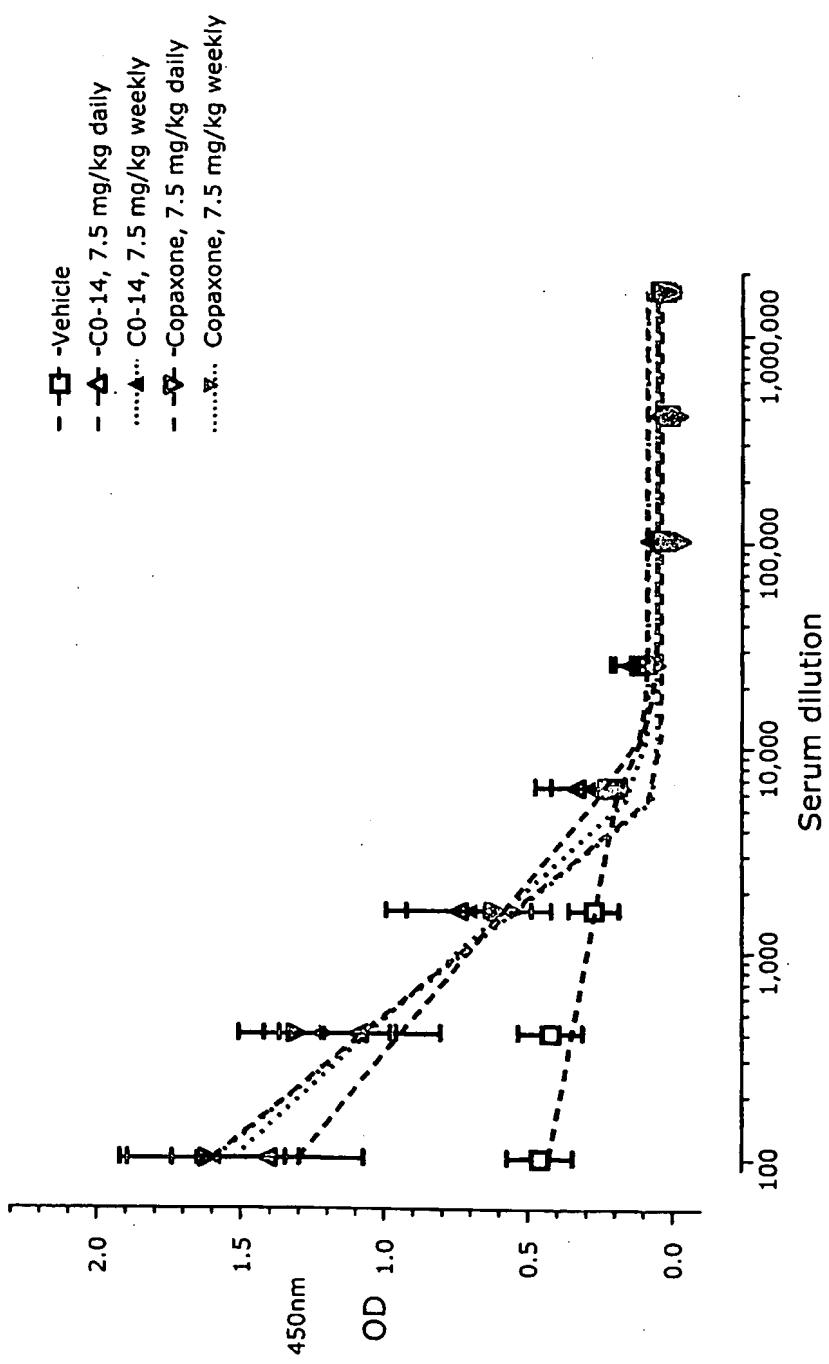


Figure 8

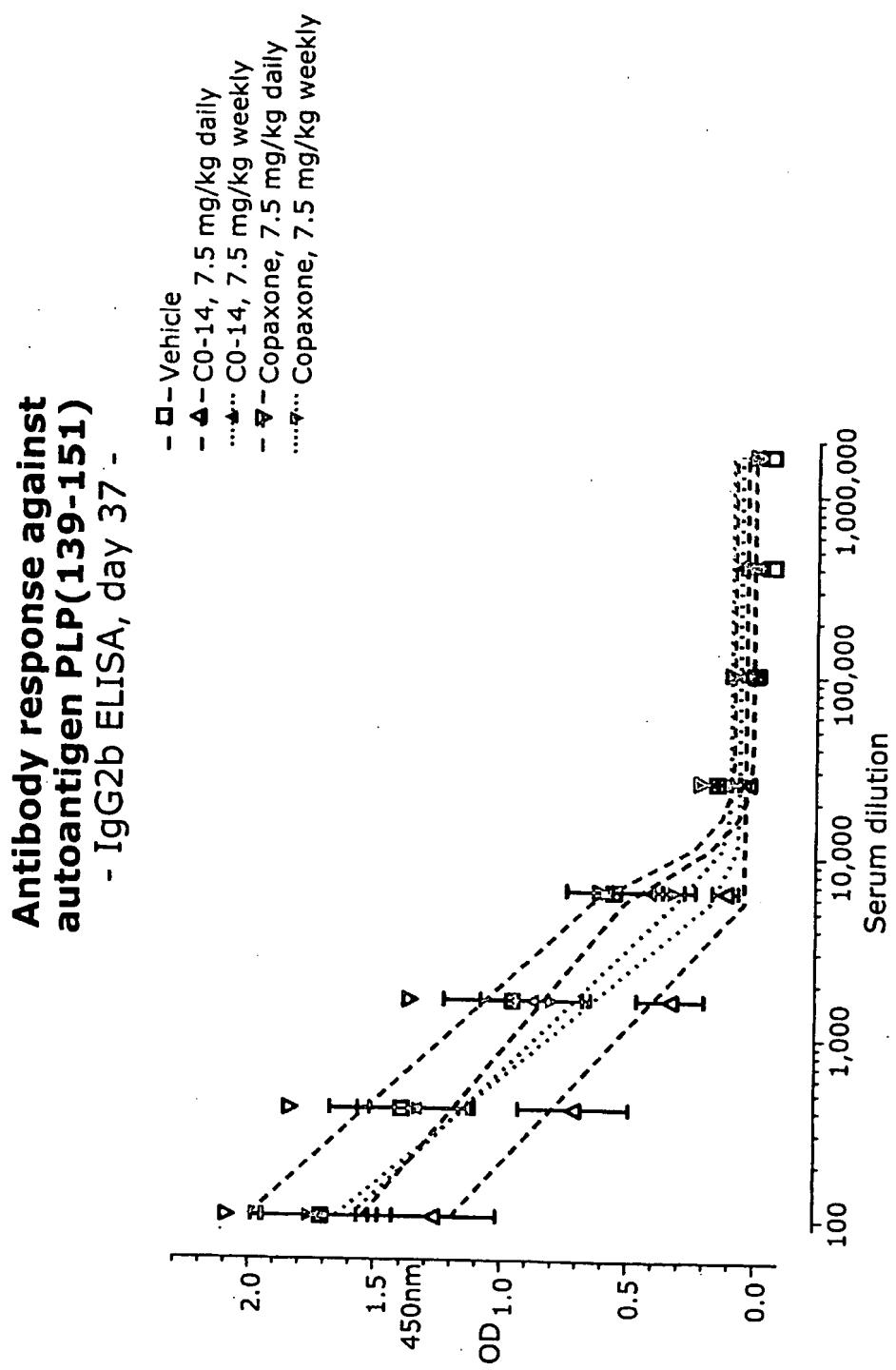


Figure 9

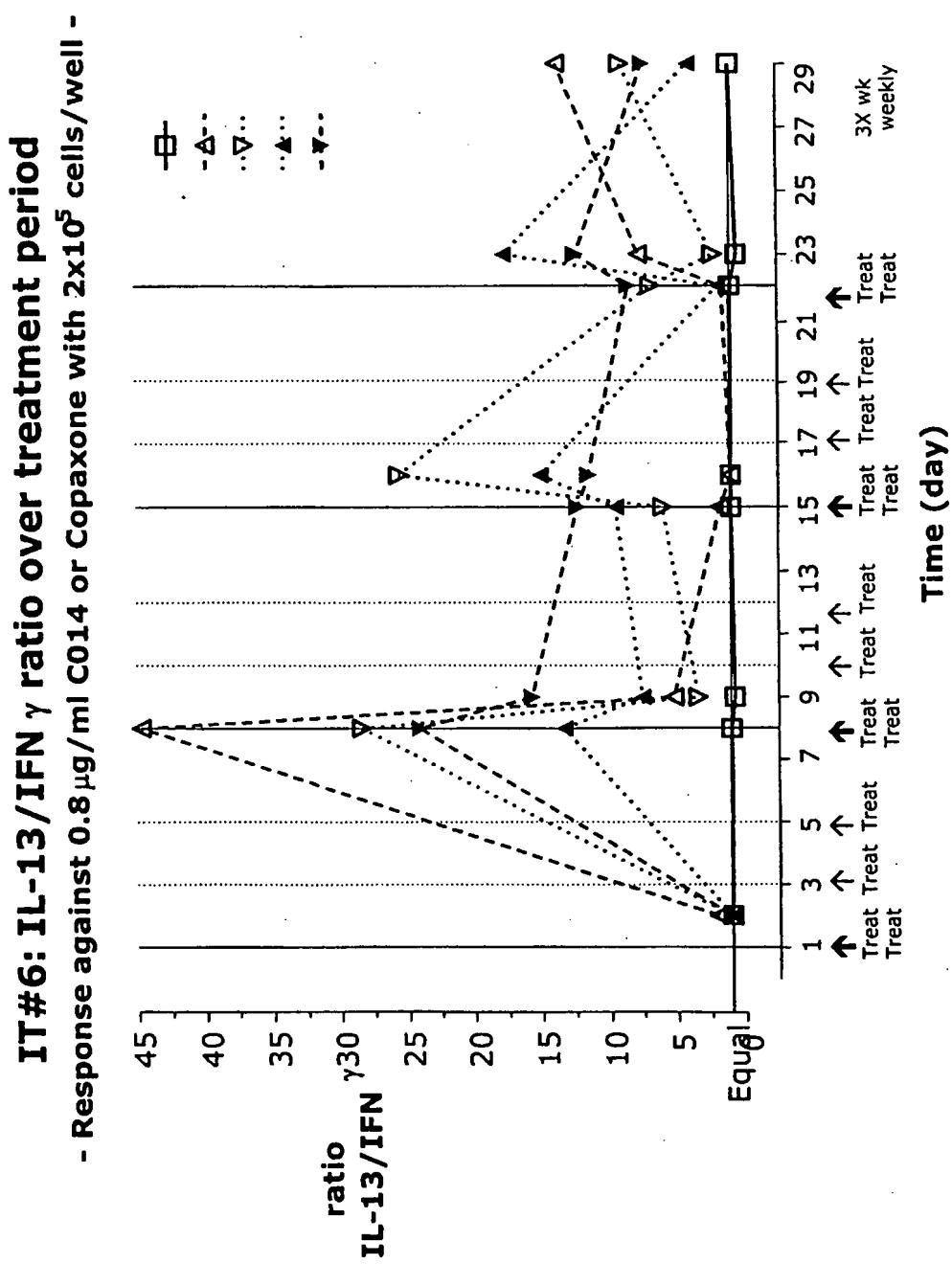
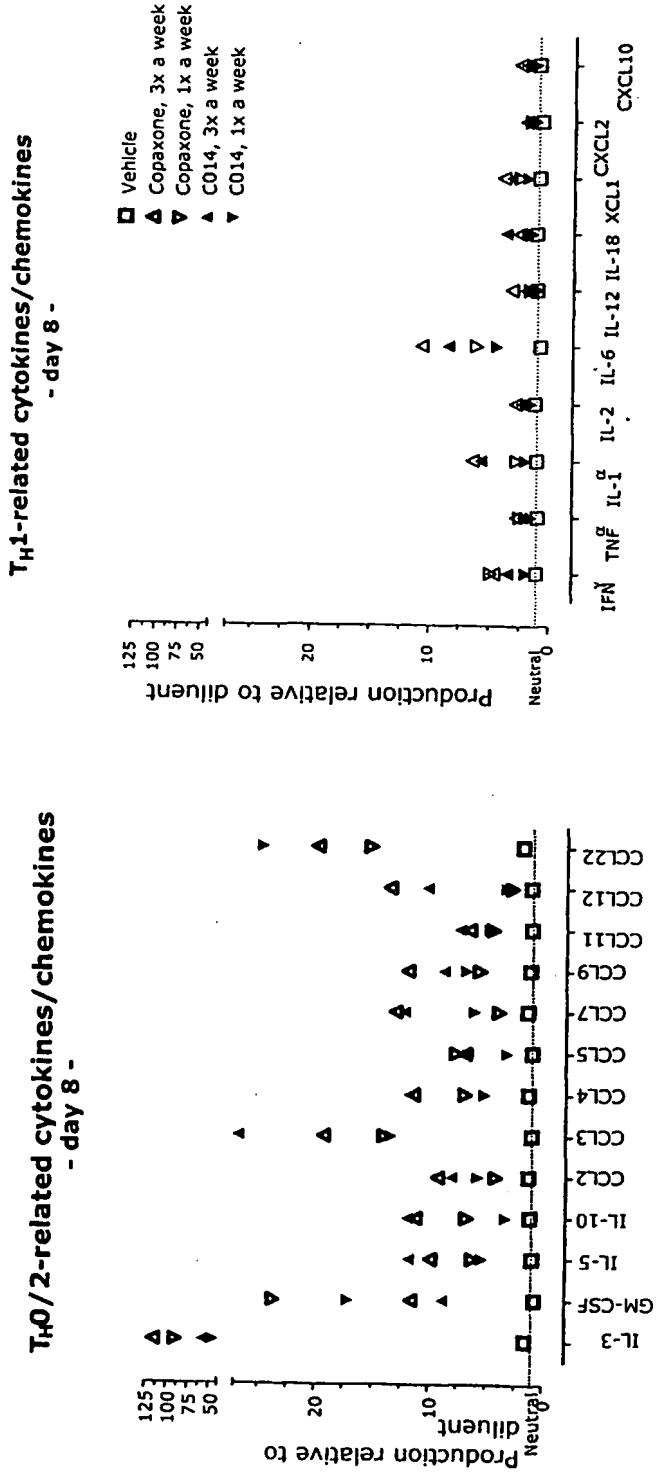


Figure 10



10/10

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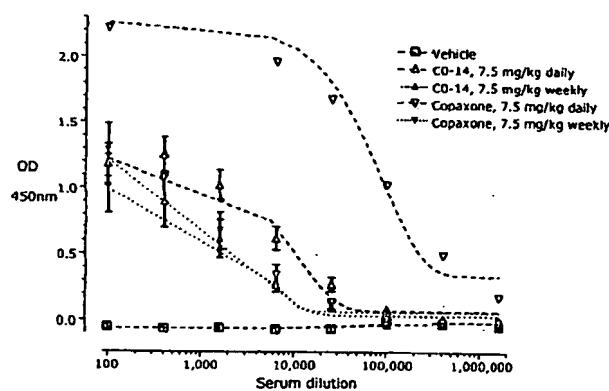
- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
26 May 2006

[Continued on next page]

(54) Title: METHODS OF TREATING DISEASE WITH RANDOM COPOLYMERS

Antibody response against respective Copolymers - total Ig ELISA, day 37 -



(57) Abstract: The invention relates to novel methods and kits for treating or preventing disease through the administration of random copolymers. The invention also relates to the treatment of autoimmune diseases, such as multiple sclerosis, and to the administration of random copolymers in treatment regimen comprising formulations that are administered at intervals greater than 24 hours, or to sustained release formulations which administer the copolymer over a period greater than 24 hours. The invention further relates to methods for conducting a pharmaceutical business comprising manufacturing, licensing, or distributing kits containing or relating to the formulations or dosing regimens of random copolymer described herein.

WO 2005/120542 A3



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

Ref application No

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A. CLASSIFICATION OF SUBJECT MATTER

A61K38/02 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K - A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/004099 A1 (EISENBACH-SCHWARTZ MICHAEL ET AL) 2 January 2003 (2003-01-02) cited in the application paragraph '0091! - paragraph '0097!; examples paragraph '0110! - paragraph '0116! ----- X	1,4-98, 101, 104-107, 110-113, 124, 127-133 1,4-98, 101, 104-107, 110-113, 124, 127-133 ----- -/-
	WO 00/27417 A (YEDA RESEARCH AND DEVELOPMENT CO. LTD; MCINNIS, PATRICIA, A; AHARONI,) 18 May 2000 (2000-05-18) cited in the application examples -----	

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

Date of mailing of the international search report

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Name and mailing address of the ISA/

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Winger, R

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/016340

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FRIDKIS-HARELI MASHA ET AL: "Novel synthetic amino acid copolymers that inhibit autoantigen-specific T cell responses and suppress experimental autoimmune encephalomyelitis." THE JOURNAL OF CLINICAL INVESTIGATION. JUN 2002, vol. 109, no. 12, June 2002 (2002-06), pages 1635-1643, XP002311466 ISSN: 0021-9738 page 1636; table 1	1,2, 4-99, 101,102, 104-108, 110-113, 115, 122-125, 127-134
X	DHIB-JALBUT SUHAYL: "Glatiramer acetate (Copaxone(R)) therapy for multiple sclerosis." PHARMACOLOGY AND THERAPEUTICS, vol. 98, no. 2, May 2003 (2003-05), pages 245-255, XP002352551 ISSN: 0163-7258 the whole document	1,4-98, 101, 104-107, 110-113, 124, 127-133
P,X	ILLES ZSOLT ET AL: "Modified amino acid copolymers suppress myelin basic protein 85-99-induced encephalomyelitis in humanized mice through different effects on T cells" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 101, no. 32, 10 August 2004 (2004-08-10), pages 11749-11754, XP002368587 ISSN: 0027-8424 abstract	2,4-72, 99,102, 104-106, 108, 110-113, 115,122, 123,125, 129-132, 134
X	WO 03/029276 A (PRESIDENT AND FELLOWS OF HARVARD COLLEGE; STROMINGER, JACK, L; FRIDKIS) 10 April 2003 (2003-04-10)	2,4-72, 99,102, 104-106, 108, 110-113, 115,122, 123,125, 129-132, 134
claims 25,27,34-50; figures; examples		
P,X	WO 2004/064717 A (YEDA RESEARCH AND DEVELOPMENT CO. LTD; AHARONI, RINA; ARNON, RUTH; KAY) 5 August 2004 (2004-08-05)	2,4-72, 99,102, 104-106, 108, 110-113, 115,122, 123,125, 129-132, 134
page 10, line 4; claims		
3		-/-

INTERNATIONAL SEARCH REPORT

national application No
PCT/US2005/016340

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/047500 A (YEDA RESEARCH AND DEVELOPMENT CO. LTD; EISENBACK-SCHWARTZ, MICHAL; YOL) 12 June 2003 (2003-06-12) page 14, line 28 - page 15, line 4; claims	2, 4-72, 99, 102, 104-106, 108, 110-113, 115, 122, 123, 125, 129-132, 134

INTERNATIONAL SEARCH REPORT

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-113 and 124-128 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1,2(part),4-72(part),73-98,99(part),101,102(part),104-106(part),107
108(part),110-113(part),115(part),122-123(part),124,125(part),127,128
129-132(part),133,134(part)
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims:

1,4-72(part),73-98,101,104-106(part),
107,110-113(part),124,127,128,
129-132(part),133

A method of treating a treatable disease with a random YEAK copolymer and pharmaceutical compositions thereof.

2. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random VYAK copolymer and pharmaceutical compositions thereof.

3. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random VWAK copolymer and pharmaceutical compositions thereof.

4. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random VEAK copolymer and pharmaceutical compositions thereof.

5. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random FEAK copolymer and pharmaceutical compositions thereof.

6. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random VAK copolymer and pharmaceutical compositions thereof.

7. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method of treating a treatable disease with a random WAK copolymer and pharmaceutical compositions thereof.

8. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random YAK copolymer and pharmaceutical compositions thereof.

9. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random FAK copolymer and pharmaceutical compositions thereof.

10. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random YEK copolymer and pharmaceutical compositions thereof.

11. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random ELSA copolymer and pharmaceutical compositions thereof.

12. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random DLYV copolymer and pharmaceutical compositions thereof.

13. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random KEASV copolymer and pharmaceutical compositions thereof.

14. claims:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

3,4-72(part),100,103,104-106(part),
109,110-113(part),116,122-123(pa-
rt),126,129-132(part),135

A method of treating a treatable disease with a random copolymer with a plurality of residues and pharmaceutical compositions thereof.

15. claims: 114,117-121

A kit comprising a random copolymer YFAK.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/016340

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
US 2003004099	A1	02-01-2003		AT 302020 T AU 780188 B2 AU 3451701 A CA 2397785 A1 CN 1427726 A DE 60112718 D1 DK 1248643 T3 EP 1248643 A2 ES 2243450 T3 JP 2003520246 T MX PA02007106 A PT 1248643 T WO 0152878 A2	15-09-2005 03-03-2005 31-07-2001 26-07-2001 02-07-2003 22-09-2005 07-11-2005 16-10-2002 01-12-2005 02-07-2003 13-12-2002 31-10-2005 26-07-2001
WO 0027417	A	18-05-2000		AU 775073 B2 AU 1727000 A CA 2355400 A1 EP 1128839 A1	15-07-2004 29-05-2000 18-05-2000 05-09-2001
WO 03029276	A	10-04-2003		CA 2462459 A1 DE 02800437 T1 EP 1438061 A2 HU 0401863 A2 JP 2005511518 T NO 20041345 A NO 20041759 A ZA 200402601 A	10-04-2003 11-11-2004 21-07-2004 28-12-2004 28-04-2005 31-03-2004 29-04-2004 12-05-2005
WO 2004064717	A	05-08-2004		AU 2004206120 A1 CA 2513567 A1 EP 1592384 A2	05-08-2004 05-08-2004 09-11-2005
WO 03047500	A	12-06-2003		AU 2002353486 A1 CA 2469092 A1 CN 1617736 A EP 1429800 A2 HU 0500039 A2 JP 2005515198 T	17-06-2003 12-06-2003 18-05-2005 23-06-2004 29-03-2005 26-05-2005